

Topical idoxuridine for treatment of genital warts in males. A double-blind comparative study of 0.25% and 0.5% cream

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Abstract

Fifty heterosexual male patients with histologically verified genital warts of short duration (<3 months) were randomly allocated to treatment with either 0.25% or 0.5% idoxuridine cream. The application of the cream to the warts was performed twice daily for an initial period of 14 days, whereafter patients with partial improvement or no response were retreated in the same way for another period of 14 days. Patients not completely healed after 28 days were regarded as treatment failures and withdrawn from the study. After the initial treatment period of 14 days, 19 of 25 patients (76%) treated with 0.5% idoxuridine cream, and 9 of 25 patients (36%) treated with 0.25% idoxuridine cream were completely healed. This difference is significant ($p < 0.01$). The corresponding figures at the second follow-up examination (28 days after start of the study) were 19 of 25 (76%) and 13 of 25 (52%), respectively. At the last follow-up examination three months after start of treatment, four patients treated with 0.5% idoxuridine cream and five patients treated with 0.25% idoxuridine cream had a relapse. Thus, the overall rate of complete healing was 15 of 25 (60%) for the patients treated with 0.5% idoxuridine cream and 8 of 25 (32%) for those treated with 0.25% idoxuridine cream. The difference is significant ($p < 0.01$). No adverse reactions were observed or reported by the patients.

The traditional treatment for genital warts is one weekly topical application of 20% podophyllin solution in ethanol.¹ This treatment has many disad-

vantages; it is not very effective, local toxic reactions are frequent, it is time-consuming, and inconvenient to the patients as self-treatment can not be recommended. An alternative treatment, 0.5% podophyllotoxin solution was recently introduced, and has proven to be clinically more effective than podophyllin,¹ and is more convenient since self-treatment is usually comparatively easy for males. However, podophyllotoxin also causes frequently local toxic reactions, although usually of a milder nature than podophyllin.

Surgery, carbon dioxide laser therapy and cryotherapy are also widely used, but have so far not been found to be more effective than podophyllotoxin. The use of interferons is still in an experimental stage, since optimal dosage and optimal length of treatment remain to be established. In conclusion, conventional and more recent therapies for condylomata acuminata have given inconsistent results and no one method appears to be clearly superior to another.

Since 1984, several reports have indicated that topical application of 0.25% idoxuridine (5-iodo-2-deoxyuridine) cream is effective in the treatment of vulvar condyloma acuminatum.²⁻⁴ Idoxuridine inhibits normal deoxyribonucleic acid (DNA) biosynthesis in mice and men and is a specific inhibitor of virus DNA.⁵ Idoxuridine has been extensively used for topical treatment of herpes simplex infections, especially in ophthalmology, and one major benefit is the complete absence of toxic reactions.

The aim of the present study was to evaluate the therapeutic efficacy of two different concentrations of idoxuridine cream in the treatment of genital warts in male patients.

Patients and methods

Fifty male patients with condylomata acuminata were entered into the study (table 1). The diagnosis was histologically verified in all patients. The warts were of short duration in all cases, first diagnosed less than three months before start of study medication. All patients had warts localised to penile mucosa and/or skin. More than half had previously been treated

Table 1 Clinical data of the patients

	Treatment	
	0.25% Idoxuridine cream	0.5% Idoxuridine cream
No treated	25	25
Mean age (years)	27.4	26.3
Mean duration of warts (months)	2.0	1.6
Previous treatment:		
None	11	9
Podophyllotoxin	11	14
Carbon dioxide laser	3	2
No with a steady partner	12	14
No of symptomatic partners	11	10

with either podophyllotoxin or carbon dioxide laser, but had experienced a relapse a few weeks after treatment. Approximately half of the patients had a steady partner, and most of the partners also had genital warts.

All patients were heterosexuals and in good health. The warts were in all cases multiple, varying from six to more than thirty. Individual warts varied from two to ten mm in size. None of the patients had a concomitant sexually transmitted disease.

The study was carried out under a double-blind comparative design. The patients were randomly allocated to one of two treatment groups. One group was treated with 0.25% idoxuridine cream (O/W vehicle) and the other one with 0.5% idoxuridine in the same vehicle. The patients were instructed to apply the medication twice daily for two weeks. Follow-up examinations were carried out two, four and twelve weeks after the start of therapy. Patients, not completely healed at the first follow-up visit, were retreated for two more weeks. If complete healing had not been achieved at the second follow-up visit, the patient was regarded as a treatment failure, withdrawn from further study participation and transferred to other therapy. Patients with new warts at the third follow-up examination (relapse or possible reinfection) were also regarded as treatment failures.

For the purpose of statistical analysis, the treatment result was defined as *Cured* (all warts had disappeared) or *Not Cured* (incomplete response or relapse), and Mann-Whitney U-test was used for statistical significance test of the differences between the treatment groups.

Approval for the conduct of the study was obtained from the Ethical Committee of the clinic and the Finnish Board of Health prior to study start, and written information regarding the study was given to all patients. An oral informed consent for participation was obtained from all patients before start of treatment.

Results

Clinical and histological features of the warts before

Table 2 Examination results before treatment

	Treatment	
	0.25% Idoxuridine cream	0.5% Idoxuridine cream
No treated	25	25
Lesion site:		
Mucosa only	17	20
Skin only	2	2
Both mucosa and skin	6	3
Lesion type:		
Exophytic only	14	20
Flat only	6	4
Both exophytic and flat	5	1
Histological classification:		
Condyloma acuminatum	18	21
Condyloma planum	7	4
Atypical changes	3	4

start of treatment are presented in table 2. The majority of the patients in both groups had warts located only to the mucosa. About one third of the patients in the 0.25% idoxuridine cream treatment group had warts located only to the skin or to both skin and mucosa, whereas the corresponding proportion of the patients in the 0.5% idoxuridine cream group was one fifth. The number of patients with only exophytic warts was considerably higher in the 0.5% idoxuridine treatment group, but in the comparative group the number of patients with both exophytic and flat warts was higher. In the 0.25% group more patients had flat warts (totally 11, compared with 5 in the 0.5% group). A few patients in both groups were found to have mild atypical changes in the epithelia as shown by histological examination.

The follow-up examination results are presented in table 3. After 14 days of treatment approximately one third of the patients treated with 0.25% cream, and about three out of four of the patients treated with 0.5% cream were found to be completely healed. The difference reached a significant level ($p < 0.01$). At the second follow-up examination two weeks later 13 (52%) of the patients treated with 0.25% idoxuridine cream and 19 (76%) of the

Table 3 Result of treatment

	Treatment	
	0.25% Idoxuridine cream	0.5% Idoxuridine cream
No treated	25	25
No healed at first follow-up examination	9 (36%)	19 (76%)
No healed at second follow-up examination	13 (52%)	19 (76%)
No healed at third follow-up examination	8 (32%)	15 (60%)
No with relapse at third follow-up examination	5/13 (39%)	4/19 (21%)

Table 4 Treatment failures, lesion site and type

	Treatment	
	0.25% Idoxuridine cream	0.5% Idoxuridine cream
No of failures	17	10
Lesion site:		
Skin	8	0
Mucosa	9	10
Lesion type:		
Exophytic	14	8
Flat	3	2

patients treated with 0.5% cream had a complete response. This difference did not reach significance. Patients with an incomplete response after totally 28 days of treatment were considered as treatment failures, withdrawn and transferred to some other therapy. At the last follow-up examination, at three months after the start of the study, 8 (32%) of the patients in the 0.25% treatment group and 15 (60%) of those in the 0.5% treatment group were still healed. The difference is statistically significant ($p < 0.01$).

Lesion site and type in the patients with treatment failure are shown in table 4. The majority of these patients had exophytic warts located to the mucosa.

No symptoms or signs of local toxic reactions attributable to the treatment were observed by the investigators or reported by the patients.

Discussion

The results of the present study confirm previous reports indicating that topical treatment of genital warts of short duration with idoxuridine is clinically effective.²⁻⁴ However, only vulvar condylomata have been treated and a 0.25% cream has been used. Our results clearly show that this concentration is less efficient in the treatment of male patients with penile condylomata. We compared 0.5% and 0.25% idoxuridine creams, applied topically twice daily to warts

for 14 days, in male patients with either exophytic or flat warts or both types localised on mucosa and/or skin. The higher concentration of idoxuridine cream, 0.5%, was significantly more effective after 14 days of treatment. As patients showing incomplete or no response to the treatment were retreated for a further period of 14 days, the difference was less pronounced 28 days after the beginning of the study. However, at the last follow-up examination, three months after start of treatment, the difference in clinical efficacy of the two concentrations used was again significant in favour of the 0.5% cream.

Since none of the two tested idoxuridine creams caused any toxic reactions, the present results suggest that idoxuridine 0.5% cream may be considered to be a good alternative for local treatment of penile genital warts. The healing rate compares well with other current therapies, and the cream used in this study was easy to apply by the patients themselves. A similar study is under progress to evaluate whether idoxuridine 0.5% cream is more effective than 0.25% cream also in the treatment of vulvar condylomata.

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